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(81) Designated States: AU, BG, CA, CS, FI, HU, JP, KR, NO, NZ, PL, PT, RO, RU, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(54) Title: DRUG FORMULATIONS FOR PARENTERAL USE

(57) Abstract

This invention relates to parenteral preparations of antiestrogens such as toremifene, desmethyl toremifene, tamoxifen or desmethyltamoxifen. The preparations can be emulsions, liposomes or aqueous solutions of cyclodextrin-drug complexes. Particularly the invention relates to a parenteral drug formulation comprising a complex having a 2-hydroxypropyl cyclodextrin component and including an active drug substance selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof, said complex being present either in an aqueous solution or emulsion or loaded into a liposome.

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(57) Abstract

This invention relates to parenteral preparations of antiestrogens such as toremifene, desmethyl toremifene, tamoxifen or desmethyltamoxifen. The preparations can be emulsions, liposomes or aqueous solutions of cyclodextrin-drug complexes. Particularly the invention relates to a parenteral drug formulation comprising a complex having a 2-hydroxypropyl cyclodextrin component and including an active drug substance selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof, said complex being present either in an aqueous solution or emulsion or loaded into a liposome.

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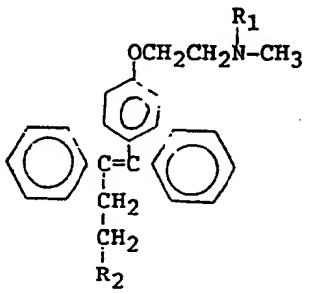
Drug formulations for parenteral use

This invention relates to drug formulations of antiestrogens, particularly antiestrogens comprising a triphenylbutene moiety, for use in parenteral administration.

Toremifene, desmethyl toremifene, desmethyl tamoxifen and tamoxifen are all examples of substituted triphenylbutenes useful in cancer therapy. Reference is made to US 4696949, US 4990538 and US 4356516. They can all be described with the formula



in which R_1 is CH_3 or H and R_2 is H or Cl.

The compounds mentioned above have the following values of R_1 and R_2;

	R_1	R_2
toremifene	CH_3	Cl
desmethyl toremifene	H	Cl
tamoxifen	CH_3	H
desmethyl tamoxifen	H	H

A common feature of these antiestrogens is their poor solubility in water. Thus, parenteral administration of these drugs cannot be accomplished simply by an aqueous solution of the active ingredients.

There is a clear need for parenteral formulations of the anticancer antiestrogens. Injectable high-concentration toremifene formulations will have important clinical benefit

1) in the attempts to reach high concentrations in tissue. This is necessary especially when combinations of toremifene with cytotoxic drugs are given to a

patient. As shown by DeGregorio et al (J Clinical Oncology, vol 7, No 9,1989: 1359 - 1364.) high plasma concentrations are more effective in reversing multidrug resistance than low concentrations. An injectable formulation enables high peak concentrations in blood and tissues without exposing the patient to long-term treatment;

2) when given locally into a tumor. This enables a high and efficacious concentration in the tumor to be achieved;

3) when used topically in a benign estrogen-dependent lesion like cystic mastalgia, where toremifene can be injected directly into a painful cyst;

4) when spreading toremifene topically onto palpable and subcutaneous breast cancer metastases;

5) when an intravesical installation is given for the therapy of superficial bladder cancer. In this indication toremifene may well be used together with other anticancer drugs to enhance their efficacy;

6) when an intraperitoneal solution is given for the treatment of certain types of overian cancer;

7) when other topical, estrogen-dependent lesions are treated with an antiestrogen.

The parenteral drug formulations according to this invention include emulsions, aqueous solutions of cyclodextrin - drug complexes and liposomes.

Dissolution properties of drugs can be significantly improved by complexation of the drug substance with cyclodextrins. Cyclodextrins (including α, β and Γ cyclodextrins and their derivatives) are all cyclic oligomers of glucose. The

cyclodextrins can form inclusion complexes with drugs in that the drug molecule is included in the lipophile-seeking cavities of the cyclodextrin molecule. Therefore the cyclodextrins effectively solubilize lipophilic drugs into aqueous media. The use of cyclodextrins in the pharmaceutical field has been described e.g. in Drug Development and Industrial Pharmacy, 17(11), 1503-1549, 1991.

With respect to the antiestrogens mentioned above, however, no parenteral drug formulations based on complexation of the active drug substance with 2-hydroxypropyl cyclodextrins are known in the art. One object of this invention is a parenteral formulation based on a 2-hydroxypropyl cyclodextrin, preferably 2-hydroxypropyl β-cyclodextrin or 2-hydroxypropyl-Γ-cyclodextrin, complex including an active drug substance selected from the group consisting of toremifene, desmethyltoremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof, said complex being present in an aqueous solution.

Emulsions of the antiestrogens mentioned above can be made by dispersing the drug or a cylodextrin complex of said drug into a pharmaceutically acceptable emulsifier, and optionally adding a stabilizing agent.

Parenteral administration of the drugs mentioned above may also be accomplished by aqueous solutions of liposomes containing said drug or a salt thereof. Liposomes are spherical particles in an aqueous medium, formed by a lipid bilayer enclosing an aqueous compartment. The lipid surface may be either unilamellar or multilamellar. The liposomes may be loaded with either hydrophobic or hydrophilic drug substances.

Another object of the invention is a parenteral formulation based on the drug substance as such loaded into liposomes. Such liposomes can be made by dissolving the drug or drug-cyclodextrin complex together with a phospholipid component, preferably DMPG (dimyristoylphosphatidylglycerol) and/or POPC

(= 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphorylcholine), in a chloroform - methanol mixture, evaporating the solvent, dissolving the residue into water followed by homogenization. According to this invention liposomes can be made directly by dissolving the drug or the drug-cyclodextrin complex and phospholipid component directly in water without foregoing dissolving into chloroform - methanol mixture.

Another object of this invention is a parenteral formulation based on a 2-hydroxypropyl cyclodextrin, preferably 2-hydroxypropyl β-cyclodextrin or 2-hydroxypropyl Γ-cyclodextrin, complex including an active drug substance selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof, said complex being loaded into a liposome.

Preparation of the antiestrogen-2-hydroxypropyl cyclodextrin complexes:

A weighed amount of 2-hydroxypropyl cyclodextrin was dissolved into distilled water by shaking with a shaker. The so formed clear solution was equilibrated with a large excess of antiestrogen at the boiling point. After removing the almost clear solution the excess of antiestrogen started to precipitate. The solution was kept overnight at room temperature and the excess of precipitated antiestrogen was removed by centrifugation.

Measurement by HPLC of the solubility of the anti-estrogen in an aqueous solution of 2-hydroxypropyl cyclodextrin.

The fully automated HPLC apparatus (Hewlett-Packard, USA) consisted of a pump 1090, an autosampler and autoinjector (79847A) with an injection volume of 10 ul and a fixed wavelength UV detector, 280 nm (79881A). The chromatograms and peak areas were recorded with an integrator 3393. The separations were carried out at room temperature on a 35 *

4.6 mm stainless steel column (packed with 3-µm spherical octadecylsilanebonded silica particles; HS-3 C-18, (Perkin-Elmer, USA)

The mobile phase consisted of a mixture of acetonitrile : 0.05 M aqueous phosphate buffer containing 0.004 M of dimethyloctyl amine with a pH of 7.4. The flow rate was 0.8 ml/min.

Preparation of the liposomes:

1) Liposomes based on cyclodextrin - drug complexes and prepared by dissolving the components in an organic solution

2-hydroxypropyl-β-cyclodextrin (12 mg), POPC (32 mg), cholesterol (4 mg), DMPG (dimyristoylphosphatidylglycerol) (8 mg) and toremifene citrate (2 mg) were dissolved in choloroform - methanol (2:1) and evaporated. The residue was dissolved in water and homogenized by sonication (Labsonic U, 50 W). The stability of the solution was good; no turbidity was observed after one month in room temperature.

2) Liposomes based on cyclodextrin - drug complexes and prepared by dissolving and homogenizing components directly in water

2-hydroxypropyl-β-cyclodextrin (24 mg), DMPG (dimyristoylphosphatidylglycerol) (16 mg) and toremifene citrate (2 mg) were simultaneously dissolved in 2 ml water and homogenized by sonication (Labsonic U, 50 W). The final solution was as clear as the solution above. The mean particle diameter of these two solutions were about 100 nm (Nicomp 370/HPL high power laser option). The solution was stable after one week storage at room temperature.

3) Liposomes which were not based on cyclodextrin complexes

Preparation of these solutions was attempted by dissolving the components directly into water. The only composition which gave a clear or slightly opalescent solution was DMPG (16 or 32 mg), toremifene citrate (2 mg) dissolved and homogenized by sonication (50 W) in 2 ml water. The stability of the solutions were not however good enough; solutions became a bit turbid in one month storage at room temperature, e.g., the composition toremifene citrate (2 mg), DMPG (32 mg) and cholesterol (4 mg) was not able to dissolve and homogenized in 2 ml water.

These results indicate that stable liposomes cannot be achieved in the absence of a cyclodextrin component especially if the drug and phosphiolipid are mixed directly into water.

However, cyclodextrin-free liposomes can be made by mixing the ingredients first in chloroform/ethanol (2:1) as described above for the cyclodextrin-containing liposomes.

Solubility results

Formulation	Toremifene solubility mg of toremifene / ml of cyclodextrin-water soln.
500 mg β-HPC/ml of aqueous soln.	87.7
250 "	53.0
125 "	21.7
63 "	14.1
25 "	7.4
0 "	0.3

β-HPC = 2-hydroxypropyl-β-cyclodextrin

500 mg Γ-HPC/ml of aqueous soln.	125.4
250 "	61.1
125 "	36.3

Γ-HPC = 2-hydroxypropyl-Γ-cyclodextrin

	Tamoxifen solubility mg of tamoxifen / ml of cyclodextrin-water soln.
500 mg β-HPC/ml of aqueous soln.	67.4
250 "	43.3
125 "	23.5
63 "	13.3
25 "	6.1
0 "	< 1.0

	Desmethyl toremifene solubility mg of desmethyl toremifene / ml of cyclodextrin-water soln.
125 mg β-HPC/ml of aqueous soln.	21.0

The pharmacokinetics of the toremifene formulations described above, when give intravenously, resemble closely those of perorally given toremifene. However, during the first minutes and 1-2 hours the concentrations of the intravenously given drug are high, while the drug, when given per os, has not yet been absorbed completely from the gastrointestinal tract.

Preparation of emulsions:

Emulsions prepared by dissolving the drug in a commercial fat emulsion.

The commercial fat emulsion used was Emulsan® 20 % (manufacturer Leiras-Kabi Infusion Ltd., Finland). Different amounts of toremifene citrate were dissolved in Emulsan solution and homogenized by sonication (Labsonic U, 50 W). The toremifene concentrations were 10 mg/ml, 14 mg/ml and 20 mg/ml. After the homogenization the samples were filtered through the 0.2 µm, 0.45 µm and 1.2 µm filters.

The concentration of toremifene was determined from the filtrate with a spectrofotometric method using the wave length of 278 nm. The samples were dissolved in methanol and diluted in the concentration of 0.02 mg/ml.

The results are presented in the following table:

Concentration before filtration [mg/ml]	Size of the filter [µm]	Concentration after filtration [mg/ml]
10	0.2 0.45 1.2	4.4 4.0 4.4
14	0.45 1.2	4.3 3.7
20	0.45 1.2	3.6 3.6

The results show that the solubility of toremifene can be increased considerably by encapsulating the toremifene in an emulsion droplet.

Claims

1. A parenteral drug preparation in the form of an emulsion or liposome of an active drug substance selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof.

2. A preparation according to claim 1 where the drug is toremifene or its non-toxic, pharmaceutically acceptable salt.

3. A parenteral drug formulation comprising an aqueous solution of a complex which comprises a 2-hydroxypropyl cyclodextrin component and an active drug component in which the active drug is selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyl tamoxifen or a pharmaceutically acceptable non-toxic salt thereof.

4. A formulation according to claim 3 where the 2-hydroxypropyl cyclodextrin component is 2-hydroxypropyl-β-cyclodextrin.

5. A formulation according to claim 3 where the 2-hydroxypropyl cyclodextrin component is 2-hydroxypropyl-Γ-cyclodextrin.

6. A formulation according to claim 3 to 5 where the drug is toremifene or its non-toxic pharmaceutically acceptable salt.

7. A parental drug formulation comprising an emulsion or liposome comprising a complex which comprises a 2-hydroxypropyl cyclodextrin component and an active

drug component in which the active drug is selected from the group consisting of toremifene, desmethyl toremifene, tamoxifen and desmethyltamoxifen or a pharmaceutically acceptable non-toxic salt thereof.

8. A formulation according to claim 7 where the 2-hydroxypropyl cyclodextrin component is 2-hydroxypropyl-β-cyclodextrin.

9. A formulation according to claim 7 or 8 where the drug is toremifene or its non-toxic pharmaceutically acceptable salt.

10. A method of treatment of an estrogen-dependent tumor in a mammal comprising administering parenterally to said mammal an amount of a formulation as claimed in claim 1 sufficient to produce the desired effect.

11. A method of treatment of an estrogen-dependent tumor in a mammal comprising administering parenterally to said mammal an amount of a formulation as claimed in claim 3 sufficient to produce the desired effect.

12. A method of treatment of an estrogen-dependent tumor in a mammal comprising administering parenterally to said mammal an amount of a formulation as claimed in claim 6 sufficient to produce the desired effect.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 92/00339

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/135; A61K47/48; A61K9/127; A61K9/107

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	CHEMICAL ABSTRACTS, vol. 116, no. 16, 20 April 1992, Columbus, Ohio, US; abstract no. 158718p, T. LOFTSSON ET AL. 'solubilization and stabilization of drugs through cyclodextrin complexation' page 442 ;column 1 ;	1-6, 10-12
X	& ACTA PHARM. NORD. vol. 1991, no. 3,4, pages 215 - 217	1-6, 10-12
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* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 MARCH 1993	30. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BENZ K.F.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF CHROMATOGRAPHY, BIOMEDICAL APPLICATIONS vol. 414, no. 1, 20 February 1987, AMSTERDAM (NL) pages 192 - 196 R.D. ARMSTRONG ET AL. 'separation of tamoxifen geometric isomers and metabolites by bonded-phase beta-cyclodextrin chromatography' see the whole document	1-2, 10-12
A	WO,A,9 117 749 (BAYLOR COLLEGE OF MEDICINE) 28 November 1991 see page 1, line 5 - line 10 see page 39, line 25 - page 41, line 3	1-6, 10-12
X	FEBS LETTERS vol. 274, no. 1,2, November 1990, AMSTERDAM (NL) pages 107 - 110 H. WISEMAN ET AL. 'mechanism of inhibition of lipid peroxidation by tamoxifen and 4-hydroxytamoxifen introduced into liposomes' see the whole document	1,2 7-9
Y	DE,A,3 331 459 (FINK ET AL.) 1 March 1984 see claim 1	1,2
Y	EP,A,0 355 604 (LEDERLE (JAPAN) ET AL.) 28 February 1990 see claims 1-20	1,2
Y	FR,A,2 502 951 (SANDOZ SA) 8 October 1982 see page 24; claim 2 see page 28, line 2 - line 3	1,2
Y	WO,A,9 006 106 (PATRINOVE) 14 June 1990 see page 3, line 24 - line 36	7-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 92/00339

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 10-12 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. FI 9200339 SA 68161

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/03/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9117749	28-11-91	AU-A- 7963691	10-12-91
		EP-A- 0528975	03-03-93
DE-A-3331459	01-03-84	None	
EP-A-0355604	28-02-90	JP-A- 2138211	28-05-90
		US-A- 5004756	02-04-91
		US-A- 5182267	26-01-93
FR-A-2502951	08-10-82	CH-A- 653256	31-12-85
		CH-A- 647149	15-01-85
		AU-A- 6508486	12-03-87
		AU-B- 564570	20-08-87
		AU-A- 8233482	14-10-82
		BE-A- 892709	30-09-82
		CA-A- 1192496	27-08-85
		DE-A- 3212053	21-10-82
		FR-A- 2572933	16-05-86
		GB-A,B 2098865	01-12-82
		GB-A,B 2148711	05-06-85
		JP-A- 57181007	08-11-82
		NL-A- 8201413	01-11-82
		SE-A- 8202172	07-10-82
WO-A-9006105	14-06-90	FR-A- 2640137	15-06-90